

# Serial Electrophysiological Studies of the Heart's Excito-Conductor System in Patients with Chronic Chagasic Cardiopathy

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## OBJECTIVES

To study the evolution of lesions in conduction system using invasive electrophysiological studies (EPS), the impact of these alterations on cardiovascular events (CVE), and the frequency of these events in chronic chagasic patients.

## METHODS

Prospective study, initiated in 1979 with clinical follow-up until 2000, with the participation of 28 chronic chagasic patients that were 18 to 65 years old, with bundle branch and/or atrioventricular blocks. The patients were submitted to two EPS with a minimum interval of four years between the studies in order to assess five electrophysiological parameters that were correlated with CVE. A 24-hour Holter and echocardiogram were performed.

## RESULTS

The average follow-up time after the first EPS was 154.5 months while the interval between EPS was 107.5 months. Ages ranged from 25 to 65 years. Twenty seven patients presented complete right bundle branch block associated with a left anterior hemiblock. The echocardiogram showed alteration in twelve patients. During the 24-hour Holter and ventricular stimulation, only one patient presented sustained ventricular tachycardia (SVT). Nine presented CVE during the study and only the HV interval  $\geq 70$ ms presented a significant statistical relationship with CVE.

## CONCLUSIONS

a) The chronic form of Chagas disease presents different progressive abnormality percentages for the electrophysiological variables and WP alterations are the most common. b) Among the electrophysiological findings, only the HV interval  $\geq 70$ ms was associated with CVE. c) The incidence of CVE was 31.1% during the average follow-up period of 154.5 months.

## KEY WORDS

electrophysiological studies, cardiovascular events, Chagas' disease

Cardiovascular events (CVE) associated with Chagas disease such as SVT, sudden death, thromboembolism and late cardiac related death have been studied extensively.<sup>1-4</sup> The electrocardiogram (EKG) can show signs of significant myocardial damage, such as the presence of a complete right bundle branch block (RBBB) which may or may not be associated with a left anterior hemiblock (LAHB). The presence of inactive areas, complete left bundle branch block (LBBB), atrial fibrillation and ventricular tachyarrhythmia indicate a worse prognosis due to the extensive myocardial fibrosis found in these situations.

The electrophysiological study (EPS) and the left ventricle angiography performed on symptomatic or asymptomatic patients, with or without conduction system disorders showed worse progression in chronic chagasic patients. This progression was related to myocardial dysfunction and to a lesser extent to the presence of conduction system disorders<sup>5</sup>, probably due to the fact that myocardial dysfunction is associated with the presence of complex ventricular arrhythmia.<sup>6</sup>

Various reports have been published in relation to repeated EPS on non-chagasic patients with follow-up of conduction system changes with a maximum interval of 35 months between the studies.<sup>7,8</sup> In relation to Chagas disease, there are no documented studies with repeated EPS on the same patients with long term follow-up that records the alterations of this exam with CVE. The objective of the present study was to evaluate the evolutionary behavior of lesions in the heart's excito conductor system using invasive EPS, the impact of these alterations on cardiovascular events (CVE), and the frequency of CVE in these patients over a prolonged follow-up period.

## METHODS

This is a prospective study approved by the Ethics and Research Committee of the Institution. At the beginning of the study twenty-eight patients with the following characteristics were studied: all had at least two positive serological tests for Chagas disease, were between the ages of 18 and 65, had few or no symptoms for the NYHA functional class II, had no previous history of cardiopathies, had EKG alterations indicating bundle branch block or atrioventricular block, chest x-ray showed a cardiac silhouette within normal limits or with an increase of up to ++ (in 4+). An echocardiogram was performed during the 2<sup>nd</sup> EPS to observe myocardial contractibility and the ejection fraction. Myocardial contractibility was considered to be altered when any degree of diffused or segmental contractile abnormalities were detected. The ejection fraction was considered as altered when it was lower than 0.65. The 24-hour Holter EKG was also performed during the 2<sup>nd</sup> EPS in order to detect ventricular extrasystoles, SVT and nonsustained ventricular tachycardia (NSVT).

All patients agreed in writing to be submitted to the EPS. The beginning of the study corresponded to the date of the first electrophysiological evaluation and the patients did not take any medications that could alter the evaluated measurements. Two EPS were performed using the techniques and normal values as previously described.<sup>9,10</sup> Values were considered elevated when they were above normal during 1<sup>st</sup> and 2<sup>nd</sup> EPS or when they increased from the 1<sup>st</sup> to the 2<sup>nd</sup> study. The findings of the HV interval were subdivided in greater than or equal to and less than 70 ms to evaluate the possibility of a group with a higher risk for CVE. Elevated values found during the 1<sup>st</sup> study that were within the normal range during the 2<sup>nd</sup> study, which was observed for the AH interval and the WP caused by vagal fluctuation, were considered normal.

Ventricular stimulation was performed on all patients with extrastimulus until the refractory period was reached. A 24-hour Holter EKG and echocardiogram were performed during the 2<sup>nd</sup> EPS to observe arrhythmia and evaluate ventricular function, respectively (table I). Outpatient follow-up was made every three to six months, depending on the manifestation of symptoms.

Statistical analysis was performed using the Fisher exact probability test and statistical significance was established as  $p < 0.05$ .

## RESULTS

The patients' ages ranged from 25 to 65 years, an average of 42.3 years and a median of forty years during the 1<sup>st</sup> EPS and from 34 to 80 years, with an average of 52.2 years during the 2<sup>nd</sup> EPS. Sixteen of the patients were male. All patients except one presented a complete right bundle branch block (CRBBB), which was associated with a left anterior hemiblock (LAHB) in seventeen patients. One patient, the only one with normal QRS complexes, presented a type 1, 2<sup>nd</sup> degree AV block. The electrocardiogram pattern remained constant for the majority of patients during the study. The only significant change was the development of a total AV block in two patients, one who had CRBBB during the 1<sup>st</sup> EPS and the other who had CRBBB associated with a LAHB during the 1<sup>st</sup> EPS. One patient who had a type 1, 2<sup>nd</sup> degree AV block without an intraventricular conduction disorder developed CRBBB without any deterioration of the AV block. The average interval between the studies was 107.5 (50 to 199) months and the average follow-up duration after the 1<sup>st</sup> EPS was 154.5 (81 to 233) months.

**Cardiovascular Events** - Cardiovascular events affected nine patients (31.1%). Four suffered sudden death, four had ischemic strokes, one had SVT, one had a pulmonary embolism and three suffered cardiac related deaths. One patient presented an ischemic stroke and sudden death and those that suffered cardiac related deaths also

**Table I – Echocardiogram and 24-hour Holter of chronic chagasic patients studied**

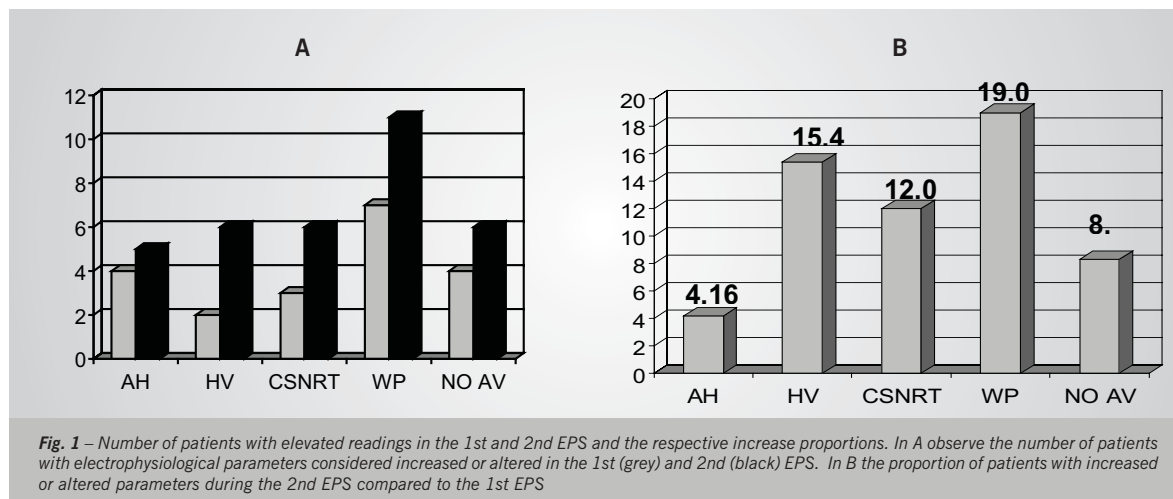
	<b>Echocardiogram</b>	<b>24-hour Holter</b>
	EF Myo contr	
1	0.61 Hypok diffuse +/4+	SR, VE POLY>30/H, TVNS
2	0.60 Hypok diffuse +/4+	SR, VE POLY>30/H, TVNS
3	0.70 NL	SR, VE POLY<30/H
4	0.70 NL	SR, VE MONO<30/H
5	0.58 Hypok infbasal	SR,VE POLY>30/H, TVNS
6	0.66 Hypok infbasal	SR, VE POLY>30/H,TVNS
7	0.77 NL	SR,VE MONO<30/H
8	0.70 NL	SR,VE POLY>30/H, NSVT
9	0.42 Hypok. diffuse +++/4+	SR, VE POLY >30/H, NSVT, SVT
10	0.69 NL	SR, VE MONO < 30/H
11	0.78 NL	SR, VE MONO < 30/H
12	0.71 NL	SR, VE POLY <30/H
13	0.74 NL	SR, VE POLY <30/H
14	0.68 NL	SR, VE POLY <30/H
15	0.65 Hypok inferior +/4+	SR, VE POLY >30/H
16	0.89 NL	SR, VE MONO<30/H
17	0.45 Hypok anteroapical+/4+	SR, VE MONO E POLY >30/H, NSVT
18	0.68 NL	SR, VE POLY<30/H
19	0.28 Hypok diffuse +++/4+	SR, VE POLY >30/H, NSVT
20	0.66 NL	SR, VE POLY <30/H
21	0.52 Hypok diffuse +/4+	SR, VE POLY<30/H, AVB 2º TYPE I
22	0.38 Hypok diffuse +++/4+	SR, VE POLY>30/H, AVB 2º TYPE I
23	0.35 Hypok diffuse +++/4+	SR, VE POLY>30/H
24	0.62 Hypok inferobasal +/4+	SR, VE POLY >30/H, NSVT
25	0.74 NL	SR, VE POLY<30/H
26	0.82 NL	SR, VE POLY >30/H, NSVT
27	0.70 NL	SR, VE POLY<30/H
28	0.76 NL	SR, VE POLY<30/H, AVB 2º TYPE I

*Hypok = Hypokinesia; VE = Ventricular Extrasystoles; Mono = Monomorphic; Poly = Polymorphic; AVB 2o degree = 2o degree Atrioventricular Block; SR = Sinus Rhythm; NSVT = Nonsustained Ventricular Tachycardia; EF = Ejection Fraction; Myo. Contr. = Myocardial Contractibility; NL = Normal; SVT = Sustained Ventricular Tachycardia*

**Table II – Description of the electrophysiological parameters collected during the 1st EPS and their correlation with CVE**

<b>EPS Parameters with CVE</b>	<b>No CVE</b>	<b>Total</b>	<b>CVE (%)</b>	<b>p Value</b>	
AH-N	7	16	23	30.4	1.00
AH-A	2	3	5	40.0	
HV-N	5	17	22	22.7	0.06
HV-A	4	2	6	66.6	
HV<70	5	18	23	21.7	0.025
HV ≥70	4	1	5	60.0	
CSNRT-N	8	14	22	36.3	0.63
CSNRT-A	1	5	6	16.6	
WP-N	6	11	17	35.2	1.00
WP-A	3	8	11	27.2	
AV Curve-N	8	14	22	36.3	0.63
AV Curve-A	1	5	6	16.6	

*A or N after electrophysiologic parameter name indicates increased/altered and normal, respectively*



suffered from another CVE (pulmonary embolism, SVT and ischemic stroke) prior to death. The data collected during the 1<sup>st</sup> EPS and the CVE are shown in table II. Figure 1 shows the alterations of the 1<sup>st</sup> and 2<sup>nd</sup> EPS and the respective proportions of increase.

**Echocardiogram** - Myocardial contractility was normal in sixteen patients and abnormal in twelve with diffused hypokinesia in seven and segmental hypokinesia in five. Of these, four were infero-basal and one antero-apical. (table I)

**24-hour Holter** - Just one patient had SVT and nine had NSVT. Fourteen patients had ventricular extrasystoles > 30/h and < 30/h. (table I).

**Electrophysiological Study** - AH interval – Five patients (17.8%) presented increases, four (14.2%) during the 1<sup>st</sup> study and two presented nonsustained CVE. The percentage of increases between the 1<sup>st</sup> and 2<sup>nd</sup> EPS was 4.16%. (table II).

HV interval – Six patients (21.4%) presented increases, two during the 1<sup>st</sup> study and four presented nonsustained CVE. The percentage of increases between the 1<sup>st</sup> and 2<sup>nd</sup> EPS was 15.38%. Five patients (17.8%) presented an HV interval  $\geq 70$  ms, four with CVE ( $p = 0.025$ ). (table II)

Corrected sinus node recovery time – Increased in six patients (21.4%), three during the 1<sup>st</sup> study and one presented nonsustained CVE. The percentage of increases between the 1<sup>st</sup> and 2<sup>nd</sup> EPS was 12%. (table II)

Wenckebach Phenomenon – Increased in eleven patients (39.2%), seven during the 1<sup>st</sup> study and four presented nonsustained CVE. The percentage of increases between the 1<sup>st</sup> and 2<sup>nd</sup> EPS was 19.04%. (table II).

Alterations in the AV node function curve – Present in six patients (21.4%), four (14.3%) during the 1<sup>st</sup> study and just one presented nonsustained CVE. The percentage of new cases with this alteration was 8.3%. (table II).

Ventricular stimulation – One patient presented SVT and five had repetitive heartbeats (table II).

## DISCUSSION

The progression of chronic chagasic cardiopathy is usually prolonged, however CVE often hasten this process. These complications are frequently associated with a histological substrate showing myocardial fiber degeneration and fibroblast proliferation with the formation of small fibrous plaques that are distributed by the myocardium. To compensate for the functional deficiency of the myocardial fibers and to maintain circulatory dynamics, the ventricles dilate.<sup>11</sup> Consequently, the size of the heart in chronic chagasic cardiomyopathy is closely related to the degree of myocardial lesion attributing to a higher incidence of CVE caused by arrhythmia<sup>12-14</sup> and thromboembolism.

Recently three-dimensional confocal microscopes have been used to detect severe diffused dilation and deformities of the arterioles which cause a perfusion of tissue that is detrimental to patients, who have had multiple heart attacks. The resulting areas of fibrosis can also cause vessel trajectory obstructions causing ischemic lesions.<sup>17</sup> Another study directly related myocardial dysfunction to the amount of interstitial myocardial collagen.<sup>18</sup>

The EPS is an important method to detail possible excito conductor system alterations in Chagas disease. Similarly, the significance of the AH interval was studied in non-chagasic patients with CRBBB associated with LAHB which revealed that an increase in this interval causes a higher incidence of organic heart disease and myocardial dysfunction.<sup>19</sup> Irregardless, follow-up during a three year period did not reveal any statistical differences in relation to the number of sudden deaths and overall mortality when compared to patients with normal and increased AH intervals. In this study, an increase in the AH interval was seen in 17.8% of the patients, which is similar to the percentages seen in non-chagasic patients<sup>19-21</sup> with no significant statistical relationship between CVE and AH interval values. Three patients presented normalization of the AH interval during the 2<sup>nd</sup> EPS probably due to vagal fluctuation.

A higher number of individuals presented a WP increase, confirming this frequent alteration in Chagas disease, which appears to be more sensitive in the identification of the conduction node disorders since the value was altered in various patients with a normal AH interval. Only four individuals presented CVE which did not have a significant statistical relationship with the increase of WP.

Conduction disorders in the His-Purkinje system are common in chagasic patients and are usually the cause of total AV block. Various studies on non-chagasic patients related an increase of the HV interval and cardiac events.<sup>19,22,23</sup> One study evaluated 517 non-chagasic individuals with a bifascicular block and an average follow-up period of 3.4 years, revealed a relationship between a prolonged HV interval and a higher incidence and severity of organic heart disease, noting that heart failure was more common with an advanced functional class rating, angina pectoris or a prior myocardial infarction.<sup>22</sup> Additionally, overall mortality and sudden death were significantly more common in the group with an increased HV interval. Two other studies with durations of three years and eight months, respectively, confirmed a higher incidence of AV block and mortality in non-chagasic individuals with these alterations.<sup>19,23</sup> However, other observations<sup>24,25</sup> did not reproduce these results. In this study of chagasic patients, the correlation between CVE and an increased HV interval was only statistically significant when calculated with HV interval values that were greater than or equal to 70ms.

Sinus node recovery time can be affected by age, associated diseases, methods employed and to a great extent by the length of the rest cycle which is why the CSNRT was used. Comparison between non-chagasic patients with bifascicular or trifascicular blocks and others with normal QRS complexes showed that the first group had a much higher percentage of electrophysiological sinus node and atrium abnormalities.<sup>26</sup> In chagasic individuals, the sinus node function was evaluated in various studies revealing variable CSNRT alteration percentages depending on the symptoms, form of disease (determined or not), the evaluation with or without an autonomic block or caused by the isolated use of atropine.<sup>5,10,27-32</sup> The mechanism of the sinus dysfunction is frequently a combination of impairment of automatism and sinoatrial conduction. Individuals with chronic Chagas disease, with or without heart failure, have significant CSNRT abnormalities ranging from 18.1% to 45%,<sup>10,31,32</sup> with the lower percentages noted in asymptomatic patients. A study of asymptomatic chronic chagasic patients with CRBBB and non-chagasic patients with CRBBB or a complete left bundle branch block revealed that an alteration in the CSNRT was an important indicator of symptomatic sinus node dysfunction; however, there was only a correlation with cardiac related mortality in non-chagasic individuals.<sup>33</sup> In this study the incidence of CSNRT alterations were proportionally similar to lower results documented in medical literature which could be due to the large number of asymptomatic patients in the

sample. The relation of an alteration in this parameter with CVE did not show any statistical significance.

At the end of the study the incidence of CVE was 31.1%. The pathophysiology of sudden death is unknown but it has been identified that chronic fibrous myocarditis, initiated and perpetrated by alterations in myocardial microcirculation and auto-immune factors, combined with autonomic nervous system lesions and left ventricular dysfunction dramatically increase the risk. A recent revision reaffirms sudden death warning signs, indicating heart rate variations and QT interval dispersion analysis as new methods of risk stratification.<sup>35</sup> None of the patients that suffered from sudden death had presented signs of decompensated heart failure, reinforcing the hypothesis that the cause was cardiac arrhythmia.

Pulmonary and systemic thromboembolisms are common in Chagas disease.<sup>4,15</sup> Generally speaking, in pulmonary thromboembolisms the embolism originates from intracavity thrombosis and not peripheral venous thrombosis. Systemic thromboembolisms are usually found in the kidneys and spleen and rarely in the brain<sup>4,15</sup> and therefore are more common in the case of an apical lesion.<sup>36</sup> In this study, four of the five thromboembolism cases were located in the brain and one in the lungs. This fact could be related to the small number of patients with decompensated heart failure which is a prerequisite for pulmonary embolism.

SVT indicates the seriousness of Chagas disease, with a five year mortality rate of almost 100%.<sup>37</sup> SVT that is induced by programmed ventricular stimulation is an important indicator of cardiac death due to arrhythmia and overall mortality in patients with nonsustained ventricular tachycardia.<sup>38</sup> Patients that present SVT with hemodynamic repercussions have worse prognoses than those that are asymptomatic or do not have SVT.<sup>39</sup> It is predominately located in the basal region followed by the septal and apical regions<sup>40</sup>, and is the arrhythmia reentrance mechanism<sup>41</sup>. In the group studied, only one patient presented SVT during the 24-hour Holter test and EPS possibly due to the large number of asymptomatic patients and also since the protocols of ventricular stimulation at the beginning of the study were less aggressive due to ethical problems.

A cardiac related death could be caused by congestive heart failure (CHF) however more common causes are malignant ventricular tachyarrhythmia or pulmonary embolisms. The three patients in this study that died from CHF had a prior history of CVE, pulmonary embolism, SVT or ischemic stroke.

Therefore, evolutionary alterations in the heart's excito conduction system are slow, progressive, and diffused which allows the identification of the seriousness and frequency of the damage to each segment, revealing which ones are related to CVE. This is valuable information for the patients, allowing a more rigorous follow-up and more frequent clinical and laboratory tests for those with the worst prognoses.

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